IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



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| In re Application of | |
| Nicholas S. BODOR | Response under 37 C.F.R. §1.116 Expedited Procedure |
| Serial No.: 06/807,034 | |
| Filed: December 9, 1985 | Art Unit: 125 |
| For: SOFT STEROIDS HAVING ANTI-INFLAMMATORY ACTIVITY | Examiner: Joseph Lipovsky |

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5/26/88
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RESPONSE UNDER 37 C.F.R. §1.116

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Reconsideration of the subject application, pursuant to and consistent with 37 C.F.R. §1.112, and in light of the remarks which follow, is respectfully requested.

At the outset, Applicant would like to thank Examiner Lipovsky for the courteous and helpful interview extended to Applicant's attorneys on January 13, 1988. During the course of that interview, Applicant's attorneys vigorously argued that the rejection of claims 1-45, 56-63 and 65-117 under 35 U.S.C. §103 over Phillipps et al (1 and 2) and Edwards in combination with Sarett et al was not a proper rejection.

Applicant maintains that the factual inquiries for establishing obviousness under 35 U.S.C. §103 as set forth in Graham v. John Deere, 383 U.S. 1 (1966), 148 U.S.P.Q. 459, have not been adequately addressed by the Examiner. Particularly, the Examiner has not completely addressed the first inquiry regarding the determination of scope and

content of the prior art or the third inquiry for resolving the level of ordinary skill in the art.

In particular, Applicant maintains that Sarett et al cannot form the basis of a rejection of the present claims since Sarett et al relate to the production of saturated and unsaturated 17α-hydroxy-2-keto-pregnane-17-carbonates. These pregnane derivatives are clearly different from the claimed androstane derivatives, especially in the absence of a hydroxyl group at the 11-position, and the presence of a $-CO-CH_2-Y$ group (Y equals halo or H), at the 17β-position. It is also worthwhile to note that these pregnane derivatives are ketone derivatives which lack an ester function (i.e., having a $-CO-O-R^1$ group at the 17β-position) of the claimed androstane derivatives.

Not surprisingly, the compounds of Sarett et al differ significantly in terms of pharmaceutical activity. Such compounds are disclosed as having progestational activity and to be valuable as esterus regulating agents. See column 1, lines 24 to 27 of the Sarett et al patent. Such activity is not even remotely related to the anti-inflammatory activity possessed by either the instantly claimed compounds or those within the Phillipps et al patents.

During the course of the interview, the Examiner agreed that if indeed that was the teaching of Sarett et al, then the rejection would not be maintained. However, the Examiner expressed concern regarding the first sentence of Sarett et al, U.S. Patent No. 3,558,675, i.e., "The invention

disclosed herein is concerned generally with novel steroid carbonates and processes for preparing them."

Applicant's representatives pointed out during the interview that that general statement was only provided as guidance to describe in general terms the general category of the compounds disclosed by Sarett et al. This sentence is only a general statement of the field of art in which Sarett et al's specific invention falls. This general type of statement is oftentimes used to assist the U.S. Patent and Trademark Office for classification purposes.

Note that the second sentence more particularly characterizes what Sarett et al perceived to be their specific invention. Indeed, all other references to steroids throughout the Sarett et al disclosure are specifically and exclusively directed to saturated and unsaturated 17α-hydroxy-20-keto-pregnane-17-carbonates. Thus, no basis is provided for extending any of the teachings of Sarett et al to Applicant's claimed androstane derivatives.

For further insight into what Sarett et al fairly disclose, Applicant obtained a copy of the file history of Sarett et al as well as the parent application, U.S. Serial No. 620,656 filed March 6, 1967. For the convenience of the Examiner, a copy of both file histories are appended hereto. Applicant would like to direct the Examiner's attention to the top half of page 3 of the Amendment filed October 31, 1968 in U.S. 620,656 wherein Sarett et al clearly characterized and limited their invention to "17α-hydroxy steroid 17-carbonates". Sarett et al argued that their compounds were "clearly distinct from" the ester compounds

known in the prior art at the time. This further supports and confirms Applicant's interpretation of the Sarett et al reference.

To clarify the level of predictability in this art, Applicant has also provided various pages from the book "Steroid Drugs" by Norman Applezweig. For the convenience of the Examiner, various passages have been highlighted. The highlighted sections on page 3 of the introduction show that minor variations in the steroid molecule can provide tremendously different properties. Further, Chapter 5, which begins on page 87, illustrates the extreme differences between progestogens and corticoids. These differences further distinguish the teachings of the Sarett et al patent from the instant claims as well as that of the Phillipps patents.

Thus, in considering the scope and content of the prior art, Applicant again categorically disputes the Examiner's statements that Sarett et al teach the "conventionality" of modifying hydroxy substituents with oxycarbonyloxy substituents at the 17α-position of the steroid nucleus. Both the file history of Sarett et al and one of ordinary skill in this art (as evidenced by the "Steroid Drugs" reference) would interpret the teachings of Sarett et al to be directed to the specific disclosed carbonates which have progestational activity. In addition, the Examiner has never shown how only one reference can show the alleged "conventionality", particularly in view of a contrary teaching within the file history of that reference.

FALSE
FILE OF PAT 3558675
CLAIMED STEROIDS
BROADLY IN GRP. CL. 1.
DISCLOSURE

The Graham v. John Deere test also requires the determination of the level of ordinary skill in the art. In an attempt to clarify this issue, Applicant believes that it is worthwhile to understand the background against which the present invention was made and the advantages obtained by the present invention. Applicant's "soft drug" approach is a marked departure from traditional drug design. This approach is based on structure/activity relationships and emphasizes the factor of safety over that of intrinsic activity. Indeed, the ways in which the toxic dose of a target compound may be reduced depend on the alteration of the disposition of the drug in the body. Previously, in the prodrug approach, the compound may be modified so that it is initially inactive but once it reaches the site of action, it becomes activated and produces its therapeutic effect. Hence, the distribution of the target compound is modified to reduce its undesired interaction with sites of action other than where it is intended. The toxicity of a target compound may be divided into its intrinsic toxicity and the toxicity of its metabolites. Intrinsic toxicity is related to its intrinsic activity, while the toxicity of its metabolites may be inactive, active or reactive. The toxicity of an inactive metabolite is zero but those of the active and reactive metabolites are not and for that reason, active and reactive metabolites are clearly not desirable.

The prior art utilizes ester groups to produce highly active compounds for dermal application. This process is the antithesis of Applicant's approach which is geared to the production of specific derivatives, e.g., of

hydrocortisone. These are produced by derivatizing known endogenous inactive metabolites of, e.g., hydrocortisone with metabolically labile biofunctional carbonate moieties. This modification produces a soft drug, which has the same order of potency but a much lower order of toxicity. Clearly, this approach is a marked departure from that of the prior art.

Moreover, the two Nakagawa Declarations previously filed in Applicant's Amendment filed September 2, 1987 illustrate the advantage of the instant invention in achieving high-inflammatory activity, while at the same time reducing toxicity/undesirable side effects.

In considering the level of ordinary skill in this art, the Examiner must consider the references he cited, in the appropriate context. In addition, other evidence regarding the level of skill in the art must be given proper consideration. Such evidence is shown by both the file history of the Sarett et al application and the book "Steroid Drugs". Further evidence is provided by the Stache et al patents. As previously discussed, these patents clearly establish that prior art steroidal esters and carbonates are not equivalent. Further, the Stache patents relate directly to anti-inflammatory "carbonate" patents and would actually lead the artisan away from Applicant's specific compounds. The discussion of the issue appears on page 6 of Applicant's September 2, 1987 Amendment.

Based upon a complete understanding of the present invention and prior art, Applicant respectfully submits that the claims cannot be properly rejected under 35 U.S.C. §103 over the Examiner's combination of the Phillipps et al

patents, Edwards and Sarett et al. As discussed during the interview, if Sarett et al does not address Applicant's claimed androstane derivatives, the rejection cannot be maintained. In particular, Applicant's overwhelming evidence regarding both the scope and content of the prior art and the level of ordinary skill in the art overcome the total lack of evidence brought forth by the Examiner. Further, the art fails to disclose or suggest either the instant claims or the unexpected advantages derived therefrom.

Also note that the Examiner's statement that the second Nakagawa Declaration is not on point since it allegedly fails to a failure to address the expected utility of compounds produced as a result of the combination of references is incorrect. The prior art provides no reasons to make the hypothetical combinations set forth by the Examiner.

As Applicant noted on page 13 of his Amendment filed September 2, 1987, only when an ester group ($-CO-OR_1$) is present at the 17β-position and a carbonate group ($-OCOOR_2$) is simultaneously present at the 17α-position, will the resulting compounds display unexpected high therapeutic indices. These unexpected results are a marked departure from the state of this art. The claimed compounds profoundly differ from those of the prior art, exhibit therapeutic indices which could not be predicted therefrom, and are consummately patentable thereover.

For the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be the next in order, and such action is earnestly solicited.

If the Examiner has any questions or helpful suggestions concerning the subject application, he is respectfully requested to telephone the undersigned at 836-6620.

Respectfully submitted,

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